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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FISHER, ABIGAIL L	

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1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/017,568	ZEMEL ET AL.	
	Examiner	Art Unit	
	ABIGAIL FISHER	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,25-27,29,35-38,41,42,46-68 and 78-80* is/are pending in the application.

4a) Of the above claim(s) *22,25-27,29,42,46-49,51-54,59,60 and 64-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-38,41,50,55-58,61-63 and 78-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/6/09, 6/3/09, 8/20/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments/Remarks filed on July 14 2009 is acknowledged. Claims 1-21, 23-24, 28, 30-34, 39-40, 43-45 and 69-77 were/stand cancelled. Claim 38 was amended. Claim 80 was added. Claims 22, 25-27, 29, 35-38, 41-42, 46-68 and 78-80 are pending. Claims 22, 25-27, 29, 42, 46-49, 51-54, 59-60 and 64-68 are withdrawn as being directed to a non-elected invention. Claims 35-38, 41, 50, 55-58, 61-63 and 78-80 are directed to the elected invention.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 3/6/09, 6/3/09 and 8/20/09 were considered by the examiner.

New Rejections Necessitated by the Amendments filed July 14 2009

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 80 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 80 introduce new matter as the claims recite the limitation: "two antagonists" of calcitrophic hormone. There is no support in the specification for this limitation. The limitation of: "two antagonists" was not described in the specification as filed, and person skilled in the art would not recognize in the applicant's disclosure a description of the invention as presently claimed. The specification discloses administration of a 1,25-$(OH)_2$-D antagonist but does not describe the instantly claimed limitation. There is no guidance in the specification to select more than one antagonist from the list of antagonists taught. Applicants have indicated support can be found at paragraphs 1, 28, 32, 35 and 37 but none of these paragraphs contemplate administration of two antagonists, one or more antagonists, or a mixture of antagonists. Therefore, it is the Examiner's position that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of filing of the instant application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 35-37 and 80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 and 35-37 as currently written are vague and indefinite. Claims 22 and 35-37 as currently written depend from claim 21. However, claim 21 is cancelled. Therefore, it is unclear how a claim can depend from a cancelled claim and furthermore, it is unclear what claim, claims 22 and 35-37 depend from. The claims will be interpreted as depending from claim 38.

Claim 80 as currently written is vague and indefinite. The claim recites a method of regulating body weight comprising administering to an "individual regulating body weight" two antagonists. It appears that applicants may be attempting to indicate an individual in need thereof. However, the claim recites an individual regulating body weight. Therefore, it is unclear if you mean an individual who desires to regulate body weight or something else. It is unclear what the second regulating body weight is attempting to define.

Modified Rejection Based on amendments in the reply filed on July 14 2009

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 38, 41, 50, 55-58, 61-63 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norman et al. (US Patent No. 6103709) in view of Xue et al. (FASEB J, 1998).

Applicant Claims

The instant application claims a method of regulating body weight comprising administering an antagonist of calcitrophic hormone (1,25-$(OH)_2$-D) activity in an

amount effective to block calcitrophic hormone activity in adipocytes of said individual, said antagonist inducing weight loss and/or increasing metabolic consumption of adipose tissue. A specific antagonist is 1β, 25-dihydroxyvitamin D_3.

The instant application claims a method of regulating body weight comprising administering to an individual regulating body weight two antagonists of calcitrophic hormone (1,25-$(OH)_2$-D) activity in an amount effective to block calcitrophic hormone activity in adipocytes of said individual, said antagonist inducing weight loss, and/or increasing metabolic consumption of adipose tissue.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Norman et al. is directed to therapeutically effective 1α, 25-dihydroxyvitamin D_3 analogues and methods for the treatment of Vitamin D diseases. It is taught that the invention covers a method for the treatment of diseases caused by a deficiency or overproduction of vitamin D_3 metabolites. These diseases include osteoporosis, parathyroid diseases which includes secondary parathyroidism and for the treatment of any other disease in which 1α, 25-dihydroxyvitamin D_3 or its prodrugs are involved (column 1, lines 24-47). Analogs of 1α, 25-dihydroxyvitamin D_3 include 1β, 25-dihydroxyvitamin D_3 which is specifically taught as an antagonist of 1α, 25-dihydroxyvitamin D_3 (column 5, lines 24-28, Figure 13 and Table I and 6). Other antagonists taught include 1β-25$(OH)_2$-epi-D_3 (table 6). It is taught that occupancy of the VDR_{mem} leads to activation of a variety of intracellular messengers. It is taught that in cells that have a VDR_{mem} linked to a calcium channel there is an increase in Ca^{2+}

(calcium) ions moving into the cells which results in an increase in intracellular calcium concentrations. Opening of the calcium channel followed by the intracellular calcium increase results in increased activities of the osteoblasts, and secretion of insulin (column 12, lines 39-59 and Figure 6). Therefore, as one can see from figure 6, the natural hormone, 1α, 25-$(OH)_2D_3$, causes an increase in intracellular calcium. It is taught that 1β, 25-dihydroxyvitamin D_3 is an antagonist of the VDR_{mem}(column 14, lines 54-55). Therefore, Norman et al. teaches that 1β, 25-dihydroxyvitamin D_3 inhibits intracellular calcium increase. It is taught that pharmaceutical compositions useful for the treatment of vitamin D disorders comprise an effective amount of the analog (agonist or antagonist) in acceptable non-toxic carriers (column 33, lines 60-65). Compositions for oral or parenteral can be prepared by dissolving, dispersing, suspending, etc. The analog in a suitable carrier such as water, saline, or other liquids (column 34, lines 45-57).

Ascertainment of the Difference Between Scope the Prior Art and the Claims
(MPEP §2141.012)

Norman et al. do not teach that the disease in which 1α, 25-dihydroxyvitamin D_3 or its prodrugs are involved is obesity or other weight related diseases. However, this deficiency is cured by Xue et al.

Xue et al. teach that intracellular calcium plays an important role in the metabolic disorder of obesity and insulin resistance (page 1392, left column first paragraph). It is taught that recent data has demonstrated that increasing intracellular calcium inhibits lipolysis in a dose dependent manner (page 1392, left column, second paragraph). Since lipolysis is the process whereby fat stored in cells is broken down, if lipolysis is

inhibited then fat is not broken down. Furthermore, it is postulated by Xue et al. that intracellular calcium plays an important role in the metabolic disorder of obesity and insulin resistance. Obese patients' exhibit elevated basal intracellular calcium levels in adipocytes and that elevating intracellular calcium results in reduced lipolysis (page 1395, third paragraph).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Norman et al. and Xue et al. and utilize 1β, 25-dihydroxyvitamin D_3 in a method of regulating weight by reducing weight gain. One of ordinary skill in the art would have been motivated to utilize 1β, 25-dihydroxyvitamin D_3 in a method of reducing weight as Xue et al. teach that an increase in intracellular calcium inhibits lipolysis which prevents stored fat from being broken. Since one of ordinary skill in the art would know from the teachings of Norman et al. that 1α, 25-dihydroxyvitamin D_3 causes an increase in intracellular calcium, it would have been obvious to one of ordinary skill in the art to administer an antagonist of 1α, 25-dihydroxyvitamin D_3 such as 1β, 25-dihydroxyvitamin D_3 in order to stop the inhibition of lipolysis caused by 1α, 25-dihydroxyvitamin D_3. Furthermore, it would have been obvious to one of ordinary skill in the art to administer 1β, 25-dihydroxyvitamin D_3 in order to control intracellular calcium as Xue et al. teach that intracellular calcium plays an important role in the metabolic disorder of obesity and insulin resistance.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Norman et al. and Xue et al. and utilize 1β, 25-dihydroxyvitamin D_3 and 1β-25$(OH)_2$-epi-D_3 in a method of regulating weight by reducing weight gain. Both 1β, 25-dihydroxyvitamin D_3 and 1β-25$(OH)_2$-epi-D_3 are taught by Norman et al. as antagonists of 1α, 25-dihydroxyvitamin D_3. Since one of ordinary skill in the art would know from the teachings of Norman et al. that 1α, 25-dihydroxyvitamin D_3 causes an increase in intracellular calcium, it would have been obvious to one of ordinary skill in the art to administer an antagonists of 1α, 25-dihydroxyvitamin D_3 in order to stop the inhibition of lipolysis caused by 1α, 25-dihydroxyvitamin D_3. Furthermore, it would have been obvious to one of ordinary skill in the art to administer the antagonists in order to control intracellular calcium as Xue et al. teach that intracellular calcium plays an important role in the metabolic disorder of obesity and insulin resistance. As a general principle it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining them flows logically from their having been individually taught in the prior art. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) **MPEP 2144.06.**

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Norman et al. and Xue et al. and formulate 1β, 25-dihydroxyvitamin D_3 into a liquid pharmaceutical composition. One of ordinary skill in the art would have been motivated to formulate a liquid pharmaceutical

composition as Norman et al. teach that this is a suitable form to administer 1β, 25-dihydroxyvitamin D_3 either orally or parenterally. It would have been obvious to one of ordinary skill in the art to formulate the 1β, 25-dihydroxyvitamin D_3 into suitable pharmaceutical composition form depending on the desired form of delivery.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norman et al. in view of Xue et al. and in further view of Jequier (Am. J. Clin. Nutr. 1987, cited in the Office action mailed on July 10 2008).

Applicant Claims

Applicant claims that the individual has Grade I, Grade II and Grade III obesity (separately claimed).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Norman et al. and Xue et al. are set forth above. Specifically, Norman et al. teach that 1β, 25-dihydroxyvitamin D_3 is an antagonist of 1α, 25-dihydroxyvitamin D_3 and can be utilized to treat vitamin D related disorders. Norman et al. additionally teach that 1α, 25-dihydroxyvitamin D_3 causes an increase in intracellular calcium. Xue et al. teach that obese patients exhibit elevated basal intracellular calcium levels in adipocytes and that elevating intracellular calcium results in reduced lipolysis.

Ascertainment of the Difference Between Scope the Prior Art and the Claims
(MPEP §2141.012)

Norman et al. do not specify administration to individuals with Grade I, Grade II, or Grade III obesity. However, this deficiency is cured by Jequier.

Jequier discloses that desirable range of a BMI for women and men is between 20-25. Grade 1 obesity corresponds to a BMI of 25-29.99. Grade II of 30-40 and Grade III greater than 40. The health risks associated with obesity include mortality, dyslipidemia, hypertension, or diabetes (page 1035, left column, 2nd and 3rd paragraphs).

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art to combine the teachings of Norman et al., Xue et al. and Jequier and administer 1β, 25-dihydroxyvitamin D_3 to individuals with Grade I, Grade II, and Grade III obesity. One of ordinary skill in the art would have been motivated to administer 1β, 25-dihydroxyvitamin D_3 to these types of individuals because they are great risk for developing diseases and even death as taught by Jequier. One of ordinary skill in the art would have been motivated to administer 1β, 25-dihydroxyvitamin D_3 to obese individuals as Xue et al. teach that obese patients exhibit elevated basal intracellular calcium levels in adipocytes and that elevating intracellular calcium results in reduced lipolysis and Norman et al. teach that 1β, 25-dihydroxyvitamin D_3 is an antagonist of 1α, 25-dihydroxyvitamin D_3 increase in intracellular calcium.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants argue that Norman teaches that 1α, 25-dihydroxyvitamin D_3 has a different effect on the three different cell types taught. 1α, 25-dihydroxyvitamin D_3 is reported to cause osteoblasts to absorb Ca^{2+} while osteoclasts release Ca^{2+}. It is argued that Norman does not disclose or suggest the claimed methods (i.e. administering an antagonist in an amount effect to block calcitrophic hormone activity in adipocytes). Therefore, it is argued, that one of ordinary skill in the art could not assume that 1α, 25-dihydroxyvitamin D_3 would have any particular effect on any given cell type because its effects are unpredictable. Applicants argue that (2) these three examples (the effect in intestinal, osteoclast and osteoblasts) demonstrate that the effect of 1α, 25-dihydroxyvitamin D_3 is cell specific and can not be generalized without experimental evidence to support the generalization. Applicants argue that (3) literature on calcium and vitamin D metabolism shows the effect on both calcium and vitamin D on body systems is unpredictable and can only be determined by experimentation.

Applicants' arguments filed July 14 2009 have been fully considered but they are not persuasive.

Regarding applicants first and second argument, firstly the examiner does not see all of these teachings applicants point to. Applicants have specifically pointed to columns 12 and 19. In column 12, it is stated that in both intestinal cells and osteoblasts there is an increase in intracellular Ca^{2+}. In column 19, it is taught that one property of vitamin D is its ability to stimulate intestinal absorption of the calcium. A second important physiological action of $1\alpha,25(OH)_2D_3$ is its effects on bone cells. Under circumstances of a dietary shortage of calcium, the blood concentration of Ca^{2+} falls and the individual becomes hypocalcemic. In order to prevent an extreme reduction in the blood concentration of calcium, the organism utilized $1\alpha,25(OH)_2D_3$ to activate bone resorbing cells, the osteoclast, which in turn mobilize bone calcium and contribute it to the blood calcium pool thereby alleviating the hypocalcemia. Applicants have focused on the osteoblasts as absorbing calcium whereas osteoclasts as releasing calcium to argue unpredictability. The examiner disagrees. Firstly, paragraph 19 states that the osteoclasts are resorbing cells. Secondly, this release of the calcium is due to a calcium deficiency. It is taught that the release is due to prevent an extreme reduction in the blood concentration of calcium. Therefore, this release is in response to a specific disease state (i.e. extreme low levels of blood concentration of calcium). Therefore, this does not suggest unpredictability of the physiological actions of $1\alpha,25(OH)_2D_3$. One of ordinary skill in the art would expect that $1\alpha,25(OH)_2D_3$ correlates to an increase in intracellular calcium and these teachings pointed to by applicant do not teach away from this. Applicants have pointed to column 24, to point out Normans teachings of transcaltachia. One section of column 24, (lines 52-59),

states utility of $1\beta,25(OH)_2D_3$ and other antagonist is based on their ability to inhibit the normal rapid action of $1\alpha,25(OH)_2D_3$ or other agonist and to block the intestinal absorption of calcium when the individual has an abnormally elevated blood concentration of Ca^{2+} in blood. Antagonists of the invention are, therefore, useful for treatment of conditions such as hypercalcemia (elevated levels of calcium). Therefore, this teaching would suggest to one of ordinary skill in the art that utilization of the antagonists can block absorption of calcium as well as elevated levels of intracellular calcium. While Norman does not suggest utilizing in adipocyte cells that is why Xue is relied upon. Xue teaches the elevated levels of intracellular calcium in adipocytes leads to reduced lipolysis. One of ordinary skill in the art would have been motivated based on the teachings of Norman to utilize antagonists in situations where there is an elevated level of intracellular calcium that one wants to reduce. Xue teaches one situation in adipocytes. While Norman does not suggest the use in adipocytes. The relationship between adipocytes, intracellular calcium levels and lipolysis was known to one of ordinary skill in the art at the time of the instant invention and one of ordinary skill in the art would have been motivated to combine the teachings of Norman and Xue, which would have achieved the instant invention.

Regarding applicants third argument, the examiner has looked over the references submitted (Appendix A-D). Applicants have not pointed to specific passages in these teachings which support their statements. Appendix A supports the notion that vitamin D is linked to intracellular cytosolic calcium (page 2018). Appendix B is directed to calcium and vitamin D supplement utilization in hip fractures. They found that there is

no evidence that calcium and vitamin D supplementation reduces the risk of fractures among community dwelling older women. It is unclear to the examiner how this supports the notion of unpredictability in vitamin D. Appendix C is directed to the relationship between calcium or vitamin D and colorectal cancer. Appendix D concludes that short-term supplementation with vitamin D and calcium improves body sway and sHPT and therefore may prevent falls and subsequent nonvertebral fractures in elderly women. It is unclear to the examiner what unpredictability these references support. Is it because Appendix B and D suggest the opposite (i.e. reduction in fractures)? If so, the examiner disagrees with this. Appendix D suggests that vitamin D and calcium can improve body sway therefore an elderly person is less likely to fall. If they are less likely to fall then there is less of a chance they are going to fracture their bones. However, Appendix B did not examine this body sway. Additionally, appendix D does not teach that elderly people wont get fractures, just that their incidence of falling was reduced and therefore reducing the risk of fracture. If the person still were to fall, the study does not state that they still won't fracture. Regardless, this data does not teach unpredictability in the art as they are directed to a variety of different disease states. An active agent may possess many different activities and the level of efficacy can vary from one disease to another. Just because the level of efficacy can vary does not mean that the field is unpredictable just that it may not be as effective in one area as compared to another. Lower efficacy does not equate to unpredictability.

The rejection is maintained as Norman teaches that $1\beta,25(OH)_2D_3$ is an antagonist of $1\alpha,25(OH)_2D_3$. Therefore, antagonists of $1\alpha,25(OH)_2D_3$ were already

known at the time of the instant invention. Norman teaches that 1α,25$(OH)_2D_3$ is associated with increase intracellular calcium levels and that 1β,25$(OH)_2D_3$ can be utilized as an antagonist to antagonize this effect. Norman teaches that the antagonists can be utilized to block or minimize the response initiated by 1α,25$(OH)_2D_3$. Norman teaches that since the deficiency or overproduction of vitamin D_3 metabolites result in serious disturbance of homeostasis, agonists or antagonists can be utilized to treat these disturbances. Xue taught at the time of the instant invention that increased intracellular calcium levels leads to inhibition of lipolysis. Therefore, when desiring to block or minimize the inhibition of lipolysis, it would have been obvious to one of ordinary skill in the art to administer antagonists, which would lead to decreased intracellular calcium levels. Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

Declaration under Rule 131

The declaration filed on July 14 2009 under 37 CFR 1.131 has been considered but is ineffective to overcome the rejection of record. Firstly, the examiner would like to note that this declaration is more appropriately a Rule 132 declaration. Secondly, the declaration is an opinion declaration and is therefore not given much weight. The declaration is written by the instant inventor Dr. Zemel and he indicates that he is of the opinion that at the time of the instant invention one of ordinary skill in the art would not have expected 1,25-$(OH)_2$-D_3 to affect lipolysis or lipogenesis in adipocytes. He opines that one of ordinary skill would have been unable to determine what effect, if any, a

vitamin D metabolite would have on the adipocyte of a person. While Dr. Zemel gives this opinion, he just states that he is of this opinion. He gives no reason or no evidence as to why one of ordinary skill would not have expected this. The declaration as a whole just gives the opinion of the instant inventor that the instant invention would not have been expected but provides no explanation or reason as why he is of this belief or any factual evidence as to why he is of this belief. Therefore, the declaration is not persuasive in overcoming the rejection of record.

Claims 35-38, 50, 55-58, 61-63 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Study: Calcium May Curb Weight Gain in Young Women (http://www.sciencedaily.com/releases/1999104199042107360 8.htm, April 21 1999, referred to in the Office action as "Science Daily", cited in PTO Form 1449) in view of Summerbell et al. (BMJ, cited on PTO Form 1449) and Jequier.

Applicant Claims

Applicant claims a method of regulating body weight comprising administering an antagonist of calcitrophic hormone (1,25-$(OH)_2$-D) activity in an amount effective to block calcitrophic hormone activity in adipocytes of said individual, said antagonist inducing weight loss, attenuating, controlling, and/or reducing weight gain and/or increasing metabolic consumption of adipose tissue. A specific antagonist is calcium.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Science Daily is directed to a study of the effect of calcium on weight gain. It is disclosed that when overall calorie consumption is account for, calcium not only helps to

keep weight in check but can be associated specifically with decreases in body fat (paragraph 1). It is disclosed that when women of the study consumed a diet of 1900 calories or less, those who consumed an average of 1000 mg of calcium per day showed an overall decrease in body weight (paragraph 4 and 5) especially when compared to women those consumed less than 1900 calories but averaged less than 780 mg of calcium per day. The women who averaged less than 780 mg of calcium actually gained body fat mass over the same period (paragraph 4). Women who received their calcium from dairy sources such as milk, yogurt and cheese showed more benefits than those who primarily used non-dairy sources such as vegetables, nuts, beans, and calcium supplements (paragraph 8). It is disclosed that women who consume calcium from dairy products or who consume at least 1000 mg per day of calcium may reap the most benefit (abstract, second paragraph).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Science Daily does not specify utilizing calcium to induce weight loss in obese women. However, this deficiency is cured by Summerbell et al. and Jequier.

Summerbell et al. is directed to weight reducing diets. The diets of the trial were directed to reducing weight in patents with a body mass index (BMI) greater than 27 (abstract). Three diets were administered. Diet 1 was a control. Diet 2 was a milk only diet. Diet three was a milk plus diet, which consisted of milk with the addition of unlimited amount of a single food (page 1488, interventions). It is disclosed that in the milk only diet patients achieved the highest overall mean weight loss (page 1489, first paragraph).

Jequier discloses that desirable range of a BMI for women and men is between 20-25. Grade 1 obesity corresponds to a BMI of 25-29.99. Grade II of 30-40 and Grade III greater than 40. The health risks associated with obesity include mortality, dyslipidemia, hypertension, or diabetes (page 1035, left column, 2nd and 3rd paragraphs).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art to combine the teachings of Science Daily, Summerbell et al. and Jequier and administer calcium to individuals with Grade I, Grade II, and Grade III obesity in regulate weight. One of ordinary skill in the art would have been motivated to administer calcium to these types of individuals because they are great risk for developing diseases and even death as taught by Jequier. One of ordinary skill in the art would have been motivated to administer calcium to obese individuals as Science Daily teach that administration of calcium causes an overall decrease in body weight. Additionally, Summerbell et al. indicates that this type of administration has been shown to induce weight loss in obese patients.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 78 is rejected under 35 U.S.C. 103(a) as being unpatentable over Science Daily in view of Summerbell et al. and Jequier and in further view of Peterson et al. (Journal of Nutrition, 1992).

Applicant Claims

Applicant claims that the form of calcium is calcium carbonate.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Science Daily, Summerbell et al., Jequier and Peterson et al. are set forth above. Specifically, Science Daily teaches that administration of calcium causes a decrease in body weight. Sources of calcium include milk, yogurt, cheese, leafy vegetables, beans, calcium supplements etc.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Science Daily does not specify that the source of the calcium is calcium carbonate. However, this deficiency is cured by Peterson et al.

Peterson et al. teach that calcium is found in spinach, nonfat dry milk, calcium carbonate, cheese, tofu, or tortillas (page 137, right column, last paragraph).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Science Daily, Summerbell et al., Jequier and Peterson et al. and utilize calcium in the form of calcium carbonate. One of ordinary skill in the art would have been motivated to utilize calcium carbonate as Science Daily teaches that administration of calcium causes a decrease in body weight

and Peterson et al. teach sources of calcium include milk, cheese, spinach as well as calcium carbonate. It would have been obvious to one of ordinary skill in the art to obtain calcium from commonly known sources such as calcium carbonate. Furthermore, Science Daily teaches that sources of calcium include milk and cheese. Therefore, one of ordinary skill in the art would have been motivated to replace milk and cheese with calcium carbonate as all are taught by Peterson et al. as functional equivalents.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants argue that (1) that Science Daily does not disclose or suggest administration to an individual regulating body weight an antagonist of calcitrophic hormone in an amount effective to block calcitrophic hormone activity in adipocytes of an individual. Applicants argue that (2) a person of ordinary skill in the art upon reading Science Daily would not draw any conclusion from its purported teachings. It is argued that a person of ordinary skill would not consider a sensational headline in a news article to constitute a teaching. Applicants argue that scientific validity of the findings. Applicants argue that (3) the Lin study shows how a person of ordinary skill in the art would have viewed an earlier reference (such as Science Daily). It is argued that the

Lin study is persuasive evidence that a person of skill in the art would conclude that Science Daily did not teach any meaningful connection between calcium and weight-related benefits. Applicants argue that (4) based upon the Summerbell article, one of ordinary skill could not determine if the weight loss is due to milk, compliance or energy deficit. This is clearly a reason for a person skilled in the art to question the meaning of Summerbell. Applicants argue that (5) Summerbell states that they don't advocate a milk only diet as a general long term reducing diet for obese outpatient where as Science Daily article reports study results obtained over a two-year period. These statements, argued by applicants would compel a person skilled in the art to conclude that the purported teachings of the Science Daily article and the Summerbell article are in conflict and would not combine the reference. Applicants argue that (6) one of ordinary skill in the art would have interpret the Summerbell article as an article about behavior, rather than about food chemistry. Any suggestion that a person of skill in the art would interpret the Summerbell study as a study of food chemistry is engaging in impermissible hindsight reasoning.

Applicants' arguments filed July 14 2009 have been fully considered but they are not persuasive.

Regarding applicants first argument, Science Daily teaches administration of calcium causes weight loss. Therefore, Science Daily teaches administration of the same claimed antagonist (calcium) in an amount that is effective for regulating body weight. The claimed antagonist produces the claimed effect which is inducing weight loss. While Science Daily does not specify that the amount is sufficient to block the

calcitrophic hormone, the amounts taught by Science Daily overlap those taught in the instant specification and the result of blocking the calcitrophic hormone (weight loss) is taught by Science Daily. Therefore, Science Daily teaches the claimed method. Note: MPEP 2112. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Regarding applicants' second argument, Science Daily specifically state that women who consumed an average of 1000 mg of calcium showed an overall decrease in body weight as high as six to seven pounds. This is a specific teaching that calcium has an effect on weight loss. While Science Daily does not specifically state how calcium works to cause weight loss, it clearly indicates that administration of calcium causes the weight loss. One way a reference qualifies as prior art is if the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country more than one year prior to date of the application of the instant application. The science daily article was a printed publication that was published more than one year prior to the earliest effective US filing date of the instant invention. Therefore, it qualifies as prior art. Furthermore, the examiner directs applicant's attention to MPEP 2121: PRIOR ART IS PRESUMED TO OPERABLE/ENABLING. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. *In re Sasse*, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). Also see MPEP 716.07. The examiner further points to

MPEP 2121.01 (II): "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." Clearly, Science Daily teaches administration of calcium causes weight loss.

Regarding applicants' third argument, Lin clearly indicates that calcium has an impact on weight regulation in women during a two year exercise intervention trial (page 757, discussion). Lin also teaches that several studies support that higher calcium intake can reduce weight (page 758,right column, second paragraph). While the applicants have pointed to section in which Lin attempts to hypothesize a rationale for the suggestion between calcium intake and weight changes, Lin et al. summarize that higher calcium intakes were associated with weight loss, specifically fat mass. Therefore, the Lin study does not dispute the assertion by the Science Daily article that calcium causes a reduction in weight. Subsequently, one of ordinary skill in the art would have been motivated to utilize calcium in a method of reducing weight by administering calcium as that is what Science Daily teaches to one of ordinary skill. While one of ordinary skill in the art may not know how calcium works to cause weight loss, one of ordinary skill in the art based on the teachings of Science Daily and Lin et al. would know that it does work. That is all that is necessary for one of ordinary skill in the art to utilize the teachings of Science Daily in combination with Summerbell et al. to administer calcium when desiring weight regulation.

Regarding applicants' fourth argument, the instant rejection is made under 35 USC 103 utilizing a combination of Science Daily and Summerbell. In response to applicant's arguments against the references individually, one cannot show

nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combination of the two references would suggest to one of ordinary skill in the art that administration of calcium to both normal and overweight individuals would lead to weight loss. While the Summerbell reference only, would not necessarily lead one of ordinary skill in the art to the idea that calcium causes weight loss. The teachings of Summerbell in combination with Science Daily would lead to this conclusion. Summerbell teaches that administration of a milk only diet to obese individuals caused weight loss. Science Daily teaches administration of calcium causes weight loss in normal weight individuals. Therefore, the teachings of Science Daily and Summerbell, when taken together, would lead one of ordinary skill in the art to administer calcium to obese individuals who desire weight regulation.

Regarding applicants' fifth argument, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The references would have suggested to one of ordinary skill in the art that administration of calcium to obese patients would cause weight loss. While the Science Daily article study was for two years and Summerbell does not advocate utilizing the milk only diet as long term reducing diet,

this teaching does not suggest that one of ordinary skill in the art would not recognize from the teachings that administration of calcium to obese patients would not cause weight loss. Furthermore, even though Summerbell does not advocate long term use, Summerbell does not preclude it from being utilized long term. This would just be a less preferable option. A less preferable option is not a teaching away, it is just less preferable. Regardless, there is no claim limitation that requires administration to be for any particular length of time. Furthermore, if there was it would have been obvious to one of ordinary skill in the art to determine the length of administration depending on the desired weight loss.

Regarding applicants' sixth argument, Summerbell is utilized to show that one of ordinary skill in the art would have been motivated to utilize the teachings of Science Daily and administer calcium to obese patients. One of ordinary skill in the art would have been motivated to administer calcium to obese patients because not only are they the patient population that need to lose weight the most but Summerbell teaches that administration of a milk only diet leads to weight loss. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Had the claims been rejected under Summerbell

only, the examiner might find this argument persuasive. However, the rejection is made over Science Daily and Summerbell. One of ordinary skill in the art would expect that the calcium in milk would have some effect based on the teachings of Science Daily. Therefore, the examiner still believes that the combination of Science Daily and Summerbell would teach one of ordinary skill in the art that administration of calcium would lead to weight loss.

Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

Double Patenting/Terminal Disclaimer

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The provisional rejection of claims 21, 23, 35-38, 50, 55-58, 61-63 and 78-79 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 10-15 of copending Application No. 10/827296 is **withdrawn** in light of the abandonment of copending '296 on April 28 2009.

The provisional rejection of claims 21, 23, 35-38, 50, 55-58, 61-63 and 78-79 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 10-17, 19-22 of copending Application No. 10/827307 is **withdrawn** in light of the abandonment of copending '307 on January 8 2009.

The rejection of claims 21, 23, 35-38, 50, 55-58, 61-63 and 78-79 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6384087 in view of Jequier is **withdrawn** in light of Applicants' filing of a terminal disclaimer on July 14 2009.

The terminal disclaimer filed on July 14 2009 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent No. 6384087 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The provisional rejection of claims 21, 23, 35-38, 50, 55-58, 61-63 and 78-79 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5-6, 28-37, 41-44, 46-53, 55, 57, 59-62, 64-72 of copending Application No. 10066057 is **withdrawn** in light of Applicants' filing of a terminal disclaimer on July 14 2009.

The terminal disclaimer filed on July 14 2009 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on Application No. 10066057 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Abigail Fisher
Examiner
Art Unit 1616

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616